WHAT IS CLAIMED:

1. A process for determining whether a test compound specifically binds to and modulates one or more cellular receptor proteins, comprising the steps of:

(a) contacting test cells co-expressing (i) a cell surface receptor protein and (ii) a neurotransmitter transport protein specific for a ligand of said cell surface receptor protein, wherein said cell produces a second messenger response upon activation of the surface protein, with (i) the test compound and a second compound known to activate the metabotropic glutamate receptor under conditions suitable for activation of the cell surface receptor protein and (ii) a control cell population wherein said cell do not express a functional cell surface receptor protein,

(b) measuring the second messenger response in the control cell population to obtain a first value and in the test cell population to obtain a second value,

(c) comparing the values obtained in (b), wherein if the second value is greater than the first value indicates that the test compound activates the target cell surface receptor protein , and wherein if the first value is greater than the second value indicating that the test compound inhibits activation of the target cell surface receptor protein.

2. The process according to claim 1, wherein said target cell surface receptor protein is a human metabotropic glutamate receptor selected from the group consisting of mGluR-1, -2, -3, -4, -5.,-6,-7 and -8.

3. The process of claim 1, wherein the second messenger response comprises change in intracellular calcium levels and the change in second messenger response is an increase in the measure of intracellular calcium in the test cell population relative to the control cell population.

4. The process of claim 1, wherein the second messenger response comprises release of inositol phosphate and the change in second messenger response is an increase in the level of inositol phosphate in the test cell population relative to the control cell population.

5. The process of claim 1, wherein the second messenger response comprises release of cyclic AMP (cAMP) and the change in second messenger response is a decerase in the level of cAMP in the test cell population relative to the control cell population.

6. The process according to claim 1, wherein said glutamate transporter protein is a murine glutamate transporter protein.

7. The process according to claim 1, wherein said metabotropic glutamate receptor is a human metabotropic glutamate receptor.

8. A mammalian cell-based assay for the profiling and screening of putative modulators of one or more human metabotropic glutamate receptor proteins, comprising:

(a) contacting a cell population comprising a plurality of cells co-expressing at least one functional human metabotropic glutamate receptor subtype or a variant, fragment or functional equivalent thereof and a functional non-human neurotransmitter transport protein or a variant, fragment or functional equivalent thereof specific for a ligand of said receptor and preloaded with a membrane potential fluorescent dye with (i) at least one modulating moiety whose ability to modulate the activity of the receptor protein is sought to be determined and (ii) a known agonist of said receptor protein ; and

(b) monitoring changes in fluorescence of the cells in the presence of the modulating moiety compared to changes in the absence of the modulating moiety to determine extent of human metabotropic glutamate receptor modulation.

9. The assay method of claim 8 in which the test cell is selected from the group consisting of MOCK, HEK293, HEK293T, BHK, COS, NIH3T3, Swiss3T3 and CHO.

10. The assay method of claim 8 in which the known agonist is added prior to, concurrently or after addition of the modulating moiety.

11. The assay of claim 9 in which the cell is an HEK293 cell.

12. The assay method of claim 8 in which a said method is used to identify a compound as one which particularly modulates an mGluR activity based on a detectable change in fluorescence.

13. The assay method of claim 8 in which said cells are seeded onto a well of a multi-well test plate.

14. The assay method of claim 8 wherein said cells are loaded with a membrane potential dye that allows for changes in fluorescence to be detected.

15. The assay method of claim 8 wherein said cell expresses at least one human mGluR subtype.

16. The assay of claim wherein a fluorescence plate reader is used to monitor changes in fluorescence.

17. The assay of claim 8 wherein a voltage imaging plate reader is used to monitor changes in fluorescence.

18. The assay of claim 8 wherein the membrane potential dye is selected from the group consisting of Molecular Devices Membrane Potential Kit (cat#R8034), Di-4-ANEPPS (Pyridinium, 4-(2-(6-(dibutylamino)-2- naphthalenyl)ethenyl)-1-(3- sulfopropyl))-, hydroxide, inner salt), DiSBACC4(2) (bis-(1,2- dibarbituric acid)- trimethine oxanol), DiSBAC4(3) (bis-(1,3-dibarbituric acid)-trimethine oxanol), CC- 2-DMPE (Pacific Blue_ 1,2-dietradecanoyl-sn-glycerol-3-phosphoethanolmine, triethylammonium salt) and SBFI-AM (1,3-Benzenedicarboxylic acid, 4,4'- [1,4,10- trioxa-7, 1 3-diazacyclopentadecane- 7,1 3-diylbis(5-methoxy-6, 12- benzofurandlyl)]bis-, tettrakis[(acetyloxy)methyl] ester; (Molecular probes).

19. The assay of claim 8 wherein said fluorescent dye is a calcium- sensitive fluorescent dye.

20. The assay of claim 8 wherein said assay is effected using an automated imaging instrument.

21. The assay of claim 8 wherein said instrument is a fluorescence plate reader (FLIPR).

22. The assay of claim 8 wherein said instrument is a voltage imaging plate reader (VIPR)

23. A method for identifying a modulator of one or more mammalian metabotropic glutamate receptor proteins, comprising:

(a) providing a cell population containing a plurality of recombinant test cells modified to contain the DNA of (i) a mammalian glutamate receptor subtype or a variant, fragment or functional equivalent thereof which is operably linked to control sequences for expression whose

activation can be coupled to Ca^{2+} signaling pathway, and (ii) a functional non-human neurotransmitter protein or a variant, fragment or functional equivalent thereof specific for a ligand of said receptor;

(b) providing at least one compound or modulating moiety whose ability to modulate the activity of a metabotropic glutamate receptor protein is sought to be determined,

(c) incubating or contacting the cell population with the modulating moiety and a calcium sensitive-fluorescent dye to form a first mixture;

(d) measuring fluorescence from the calcium-sensitive fluorescent dye in the first mixture in a fluorometric imaging plate reader (FLIPR) to obtain a first value;

(e) repeating steps a-c except to obtain a second mixture except that the cell population comprises cells that do not express a functional metabotropic glutamate receptor protein;

(f) measuring fluorescence from the calcium-sensitive fluorescent dye in the second mixture in a fluorometric imaging plate reader (FLIPR) to obtain a second value;

(g) comparing the fluorescence measurement from d) with the fluorescence measurement of f), wherein if the first value in the first mixture is greater than that of the second mixture, then said at least one test modulating moiety is a positive modulator of the metabotropic glutamate receptor protein.

24. A method for identifying a metabotropic glutamate **negative allosteric** modulator of one or more metabotropic glutamate receptor subtypes having inhibitory activity, said method comprising the steps of

(a) exposing a cell population comprising cells co-expressing at least one functional metabotropic glutamate receptor subtype or a variant, fragment or functional equivalent thereof and a functional non-human neurotransmitter transport protein or a variant, fragment or functional equivalent thereof to the candidate agent in the presence of a known metabotropic glutamate agonist, wherein said cells produces a second messenger response upon activation of the metabotropic glutamate receptor subtype, under conditions and for a time sufficient to allow interaction of the agonist with the receptor and an associated activation of the metabotropic glutamate receptor, and

(b) detecting an inhibition of the second messenger response by the agonist resulting from the interaction of the candidate agent with the metabotropic glutamate receptor subtype, relative to the second messenger response induced by the glutamate agonist alone, and therefrom determining the presence of a glutamate allosteric modulator having antagonist-like activity.

25. The process of claim 24, wherein said test cell constitutively expresses the mGluR5 receptor subtype.

26. The method according to claim 24, wherein said metabotropic glutamate receptor subtype is mGluR4.

27. A method for identifying a metabotropic glutamate **positive allosteric** modulator of one or more metabotropic glutamate receptor subtypes having antagonistic activity, said method comprising the steps of

(a) exposing a cell population comprising cells co-expressing at least one functional metabotropic glutamate receptor subtype or a variant, fragment or functional equivalent thereof and a functional non-human neurotransmitter transport protein or a variant, fragment or functional equivalent thereof to the candidate agent in the presence of a known metabotropic glutamate agonist, wherein said cells produces a second messenger response upon activation of the metabotropic glutamate receptor subtype, under conditions and for a time sufficient to allow interaction of the agonist with the receptor and an associated activation of the metabotropic glutamate receptor, and

(b) detecting activation of the second messenger response by the agonist resulting from the interaction of the candidate agent with the metabotropic glutamate receptor subtype, relative to the second messenger response induced by the glutamate agonist alone, and therefrom determining the presence of a metabotropic glutamate allosteric modulator having agonist-like or activating activity.

28. A process for screening a candidate agent for the ability of the candidate agent to positively modulate one or more metabotropic glutamate receptor subtype mediated signal transmission pathway in a mammalian cell comprising:

(a) incubating a test cell population with a candidate agent whose ability to modulate the second messenger activity of the receptor is sought to be determined, wherein said test cell: population is characterized as comprising a plurality of cell co-expresses a functional metabotropic glutamate receptor subtype glutamate receptor subtype or a variant, fragment or functional equivalent thereof and a functional non-human glutamate transport protein in or a variant, fragment or functional equivalent thereof; and wherein said cells are transformed with a recombinant DNA molecule comprising a reporter gene operably linked to a regulatory sequence which responds to a change in intracellular concentration of one or more second messenger substances of a metabotropic glutamate receptor-mediated signal transmission pathway, wherein said response is a change in the expression of a reporter gene in said test mammalian cell, said expression being indicated by production of a reporter gene product;

(b) measuring the concentration of the reporter gene product in the test cell population

(c) comparing the concentration of the reporter gene product in said test cell to the concentration of said reporter gene product in a control cell population which are identical to the test cells except that the cells of the control cell population do not express a functional metabotropic glutamate receptor subtype; wherein a higher concentration in said test cell relative to the concentration in said control cell indicates that the test substance has activating activity on said signal transmission pathway, and wherein a lower concentration in said test cell relative to the concentration in said control cell indicates that said test substance has inhibitory activity on said signal transmission pathway.

29. The process according to claim 27, wherein said recombinant DNA comprises a regulatory sequence which responds to a change in concentration of intracellular calcium brought about by modulation of said receptor.

30. The process according to claim 27, wherein said recombinant DNA comprises a regulatory sequence which responds to a change in concentration of cyclic AMP.

31. A method for identifying candidate therapeutic agents for the treatment of a metabotropic glutamate receptor mediated disorder, comprising:

(a) incubating a cell population comprising a plurality of cells co-expressing on a surface thereof at least one metabotropic glutamate receptor subtype glutamate receptor subtype or a variant, fragment or functional equivalent thereof and a functional non-human neurotransmitter transport protein or a variant, fragment or functional equivalent thereof with a test compound and a known mGluR agonist, wherein said cells comprises a reporter construct responsive to a change in one of or more second messenger substances, and wherein said reporter construct comprises a nucleotide sequence encoding a reporter protein operably linked to a responsive regulatory element responsive to a change in a second messenger resulting from activation of said receptor protein,

(b) measuring the expression of the reporter gene product in the presence of the test compound and the agonist and comparing the value to that obtained in the absence of the test compound;

(c) selecting a test compound that decreases the expression of the reporter gene product in the presence of the agonist compared to the expression of the reporter gene product in the presence of the test compound alone; and

(d) identifying the selected test compound as a candidate therapeutic agent for treatment of a neurodegenerative disorder.

32. The method of claim 31, wherein said reporter coding sequence is selected from the group consisting of a luciferase, green fluorescent protein, β-lactamase, β-galactosidase, β-glucuronidase; Alkaline phosphatase ; blue fluorescent protein, and chloramphenicol acetyl transferase.

33. A method for identifying potential allosteric modulators of a mammalian metabotropic glutamate receptor, comprising:

(a) incubating a test cell population comprising a plurality of cells co-expressing on a surface thereof at least one metabotropic glutamate receptor subtype glutamate receptor subtype or a variant, fragment or functional equivalent thereof and a functional non-human neurotransmitter transport protein or a variant, fragment or functional equivalent thereof with a known amount of a known mGluR agonist, wherein said cells comprises a reporter construct responsive to a change in one of or more second messenger substances, and wherein said reporter construct comprises a nucleotide sequence encoding a reporter protein operably linked to a responsive regulatory element responsive to a change in a second messenger resulting from activation of said receptor protein,

(b) incubating a control cell population comprising a plurality of cells co-expressing on a surface thereof at least one metabotropic glutamate receptor subtype and a non-human neurotransmitter transport protein specific for a ligand of said receptor with a known amount of a known mGluR agonist, wherein said cells comprises a reporter construct responsive to a change in one of or more second messenger substances, and wherein said reporter construct comprises a nucleotide sequence encoding a reporter protein operably linked to a responsive regulatory element responsive to a change in a second messenger resulting from activation of said receptor protein,

(c) measuring the expression of the reporter gene product in the presence of the known agonist and comparing the value to that obtained in the absence of the known agoinist but in the presence of a test compound alone;

(d) selecting a test compound that increases or decreases the expression of the reporter gene product in the presence of the test compound alone compared to the expression of the reporter gene product in the presence of the agonist alone; and

(e) identifying the selected test compound as a candidate therapeutic agent for the treatment of a neurodegenerative disease mediated by a metabotropic glutamate receptor subtype and which is susceptible to allosteric modulation by said therapeutic agent.

34. Host cells transformed with a nucleic acid construct under conditions favoring expression of at least one metabotropic glutamate receptor protein on a surface of said cells and a non-human neurotransmitter transport protein specific for a ligand of said receptor protein.

35. A process for determining whether a candidate agent is a metabotropic glutamate receptor antagonist which comprises contacting cells co-expressing a functional metabotropic glutamate receptor and a glutamate transporter protein cells with the candidate agent under conditions favoring activation of a functional metabotropic glutamate receptor, with the proviso that said cells co-express a functional glutamate transporter, and detecting any decrease in metabotropic glutamate receptor activity, as indicating that the candidate agent is a metabotropic glutamate receptor antagonist.

36. A method of screening a plurality of test compounds to identify a candidate compound which inhibits the activation of one or more human metabotropic glutamate receptor subtypes, said method comprising the step of

(a) contacting cells co-expressing at least one metabotropic glutamate receptor subtype and a neurotransmitter transport protein specific for a ligand of said metabotropic glutamate receptor subtype, wherein said cells produce a second messenger response upon activation of the metabotropic glutamate receptor, with the plurality of test compounds in the presence of a known metabotropic glutamate receptor agonist under conditions suitable for activation of the metabotropic glutamate receptor, and

(b) determining whether the extent or amount of activation of metabotropic glutamate receptor is reduced in the presence of one or more of the test compounds, relative to the extent or amount of activation of the metabotropic glutamate receptor in the absence of said one or more test compounds, and if so,

(c) separately determining whether each such compound inhibits activation of metabotropic glutamate receptor for each compound in the plurality of compounds, so as to identify any compound in such plurality of compounds which inhibits the activation of the metabotropic glutamate receptor.

37. A process for determining whether a candidate agent is a metabotropic glutamate receptor agonist which comprises contacting a control cell population comprising cells that do not express a functional metabotropic glutamate receptor protein and a test cell population comprising a plurality of cell co-transfected with nucleic acid encoding a metabotropic glutamate receptor under conditions favoring expression of the metabotropic glutamate receptor on a surface of said transfected cells and a functional glutamate transporter protein, with the candidate agent under conditions favoring activation of the metabotropic glutamate receptor and detecting any increase in human metabotropic glutamate receptor activity relative to a control cell population as indicating that the candidate agent is a metabotropic glutamate receptor agonist.

38. A process for determining whether a chemical compound specifically binds to and activates one or more metabotropic glutamate receptor subtypes, which comprises contacting cells producing a second messenger response and expressing on their cell surface at least one metabotropic glutamate receptor subtype, wherein such cells do not normally express the metabotropic glutamate receptor, with the chemical compound under conditions suitable for activation of the human metabotropic glutamate receptor and measuring the second messenger response in the presence and in the absence of the chemical compound, wherein a change in the second messenger response in the presence of the chemical compound indicating that the compound activates the metabotropic glutamate receptor subtype, with the provisio that said cell also express a glutamate transporter protein specific for a ligand bound by said metabotropic glutamate receptor subtype.

39. A cell line comprising a plurality of cells, each cell expressing on a surface thereof a functional metabotropic glutamate receptor protein and a functional non-human glutamate transporter protein (mGLAST).